PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 34638PC01	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000192	International filing date *(day/month/year)* 22.03.2004	Priority date *(day/month/year)* 21.03.2003
International Patent Classification (IPC) or national classification and IPC C12N15/11, C07H21/04, A61K31/713, A61P35/00		
Applicant SANTARIS PHARMA A/S et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 13 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.01.2005	22.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Macchia, G Telephone No. +31 70 340-4078

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000192

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-52 as originally filed

   Sequence listings part of the description, Pages

   1-4 received on 01.07.2004 with letter of 30.06.2004

   Claims, Numbers

   1-66 received on 19.07.2005 with letter of 15.07.2005

   Drawings, Sheets

   1/20-20/20 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 48-60, 62, with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 48-60, 62, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-62
	No:	Claims	63-66
Inventive step (IS)	Yes:	Claims	1-62
	No:	Claims	63-66
Industrial applicability (IA)	Yes:	Claims	1-47, 61, 63-66
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Reference is made to the following document:

D1: HAMADA M. et al.: " Effects on RNA interference in gene expression (RNAi) in cultured mammalian cells of mismatches and the introduction of chemical modifications at the 3'-ends of siRNAs " ANTISENSE & NUCLEIC ACID DRUG DEVELOPMENT, MARY ANN LIEBERT, INC., NEW YORK, US, vol. 12, no. 5, October 2002, pages 301-309.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1). Claims **48-60** and **62** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2). Document D1 discloses siRNA molecules having two nucleotides at the 3' end of the sense, antisense or of both strands substituted with ethylene-bridge nucleotides (D1: figure 3). These ethylene-bridge nucleotides of D1 are different from the LNA monomers claimed in present claim 1.

Claims **1-62** meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.

3). Document D1 teaches that the oligonucleotides disclosed in the article were synthesized by an automated synthesizer (model 394, Applied Biosystem) (D1: page 302). Synthesis of oligonucleotides by means of said model 394 automated synthesizer requires the use of tetrazole, as indicated in the reagents list for said model 394, in the Applied Biosystem website.

The subject-matter of claims **63-66** is therefore not novel (Article 33(2) PCT) and/or not inventive (Article 33(3) PCT) because the choice of the coupling times indicated in present claims 64-66 appears to falls within the obvious possibilities among which the person skilled in the art would choose, without intervention of any inventive skill, in order to solve the problem of providing a further method to synthesize oligonucleotides.

4). In addition to this, it should be remarked that the subject-matter of these claims 63-66, insofar as they relate to *a method for producing a compound comprising a strand of 12-35 nucleotide monomers, wherein said compound comprises at least one* **generic** *locked nucleic acid*, not reflecting the restriction operated in present claim 1, might not be linked by a single general inventive concept with the subject-matter of claims 1-62 (Rule 13(1) and 13(2) PCT).

5). Document D1, which is considered to represent the most relevant state of the art, discloses siRNA molecules having two nucleotides at the 3' end of the sense, antisense or of both strands substituted with ethylene-bridge nucleotides (D1: figure 3).

The subject-matter of claims **1-62** differs from the disclosure of D1 in that compounds as described in said claims, compositions, uses and methods related thereto are concerned.

The problem to be solved by the present invention may therefore be regarded as the provision of further double stranded compounds, to be used as therapeutical agents.

The solution proposed in claims **1-62** of the present application is considered to involve an inventive step (Article 33(3) PCT) because document D1 shows that " replacement of 2-nt 3' overhangs with eT, ... , abolished RNAi " (D1: page 305). Therefore, document D1 does not encourage the person skilled in the art to test further LNA-containing double-stranded RNAs to be used for gene silencing.

6.1). The industrial applicability of the subject-matter of claims **1-47, 61** and **63-66** is acknowledged (Article 33(4) PCT).

6.2). For the assessment of the present claims **48-60** and **62** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/042046	21 May 2004	6 November 2003	6 November 2002 15 May 2003